REMARKS

Claims 1-35 are pending. Claims 19 and 24 are amended to correct clerical errors. Claim 27 is amended. Support for this amendment appears throughout the specification and claims as originally filed, including at page 5, lines 1-11. No new matter is introduced by this amendment.

Applicants also wish to bring to the Examiner's attention the existence of co-pending and co-owned application Serial Number 10/349,194, which is a continuation of the instant application and similarly to the instant application claims benefit as a continuation-in-part application of co-pending and co-owned application Serial Number 09/853,304.

Rejection under 35 U.S.C. § 103(a)

Claims 1-12 and 27-35 are rejected as being obvious over Schutt (US 4,248,861). In the Action, it is stated that "[w]hile the reference does not teach the complete range, differences in concentration will not support patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical"; then it is asserted that the instant claims are obvious in that "absent a clear showing of criticality, the determinations of particular concentrations is within the skill of the ordinary worker as part of normal optimization." Applicants traverse the rejection.

The assertion fails to recognize two points with respect to Applicants' claimed subject matter. First, Applicants have established the criticality of three specific kavalactones; kawain, dihydrokawain, and dihydromethysticin, and combinations of them, that provide superior therapeutic effect for IL-12 modulation, including treatment of pain. See, Specification at page 6, lines 7-11, and Figure 1. As seen in Figure 1, the IL-12 inhibitory activity of the six most prevalent (of more than 16 kavalactones that are present in kava kava extract generally, and that extract described in Schutt) kavalactone compounds found in kava kava extract. Of the six kavalactones tested, yangonin, methysticin and desmethoxyyangonin demonstrated virtually no inhibitory activity, at 70 μg/mL or less, and limited activity at higher concentrations. In those instances the inhibitory concentration curves are generally at or below 0% in the graph in Figure 1. In contrast, the IL-12 inhibitory activity of dihydrokawain, dihydromethysticin and kawain

were consistently much superior across the entire concentration range tested. As illustrated in the graph in Figure 1, the inhibitory curve for those three compounds was significantly well above 0%, and more importantly, significantly higher that the other three kavalactones; yangonin, methysticin and desmethoxyyangonin. These results clearly indicate the heretofore-unrecognized superior IL-12 inhibitory activity of dihydrokawain, dihydromethysticin and kawain, alone or in combination. The cited art provides no recognition of this result.

Second, the Schutt compositions contain 0.5 to 3 parts kava kava extract. Kava kava extract includes a number of various kavalactones, i.e. more than sixteen. Of these, kawain, dihydrokawain, and dihydromethysticin make up about 40% - 60% of the total kavalactone content. Thus, Schutt describes compositions having about 0.006% – 0.4% (i.e., < 1%) total content of those three kavalactones. Such compositions are distinguishable from, and are not suggestive of, Applicants' medicinal ointment compositions (i.e., those having 1% - 90% content of those three kavalactones) used in their claimed methods for treating pain. Nowhere in the Action is evidence provided regarding the motivation for one of ordinary skill in the art, reading Schutt, to arrive at Applicants' claimed subject matter.

The superior and surprising inhibitory effect of a specific single kavalactone (i.e., kawain, dihydrokawain, or dihydromethysticin), or a combination, of kawain, dihydrokawain, and dihydromethysticin in methods of treating pain, was not heretofore recognized. Schutt provides no teaching of any one particular kavalactone, nor any specific combination (other than the combination of all 16+ kavalactones that happen to be in natural extract in the proportions typical of such extracts) of kavalactones. Based on the foregoing, Applicants submit that the claimed subject matter is not rendered obvious in light of Schutt and respectfully request withdrawal of this rejection.

Claim 27, which claims a method using a medicinal ointment comprising active kavalactone selected from desmethoxyyangonin, dihydrokawain, dihydromethysticin, kawain, methysticin, and yangonin, is amended to recite an ointment essentially devoid of para-aminobenzoic acid. Schutt discloses compositions requiring (amongst various other required agents) para-aminobenzoic acid. Schutt does not provide for compositions devoid of

para-aminobenzoic acid. As Applicants' claim 27, as amended, recites compositions essentially devoid of para-aminobenzoic acid, Applicants submit that the claimed composition is not rendered obvious in view of Schutt. Applicants therefore respectfully request withdrawal of this rejection.

Claims 13-20 are rejected as being obvious over Asmussen (US 6,379,696) in combination with Elbakyan (WO 00/30578) further in combination with Schwabe (US 5,296,224) and further in combination with Schutt. It is stated in the Action that: (i) Asmussen, while teaching a patch, does not expressly teach the patch composition or that kawain is used to treat pain; (ii) Elbakyan, while teaching a transdermal patch composition, does not expressly teach a kavalactone as an active agent; (iii) Schwabe, while teaching that kawain is a kavalactone, does not expressly teach that kavalactones treat pain; and (iv) that Schutt teaches a topical composition comprising kava kava extract that contains the specific kavalactones and is used for anesthetic effect. It is then alleged that it would have been obvious to one of skill in the art to prepare a transdermal system of claims 13-20 because Asmussen teaches kawain in a transdermal system, Elbakyan teaches a transdermal patch, Schwabe teaches suitable kavalactones and Schutt teaches kavalactones to treat pain. Applicants traverse the rejection.

Similarly to that delineated above, Applicants' have discovered three specific kavalactone compounds (i.e., kawain, dihydrokawain, and dihydromethysticin) and combinations thereof that possess superior and unexpected IL-12 inhibitory activity. This superior activity is illustrated in Figure 1 and is stated in Applicants' Specification at page 6, lines 7-11. None of Asmussen, Elbakyan, Schwabe, Schutt or any combination of them, teaches or suggests the use of the specifically claimed compounds (i.e., kawain, dihydrokawain, and dihydromethysticin) or combinations thereof in the claimed amounts for treating pain. Schwabe provides no indication whatsoever of the advantage of any particular kavalactone or its activity against IL-12 or pain. Schutt only describes kava kava extract generally. Schutt provides no teaching of any one particular kavalactone, nor any specific combination (other than the combination of all 16+ kavalactones that occur in natural extract in the proportions typical of such extracts) of kavalactones for a particular purpose.

Based on the foregoing, Applicants submit that none of Asmussen, Elbakyan, Schwabe, Schutt (or any combination thereof) provides a teaching or suggestion of Applicants' unexpected and superior result: methods of treating pain using one or a combination of three specific kavalactones (i.e., kawain, dihydrokawain, and dihydromethysticin) that have superior IL-12 inhibitory activity in the claimed amounts. None of the cited art references provides any indication of the suitability of the specifically identified compounds, the specific amounts of those three compounds (which is separate and distinct from that in the Schutt compositions), their IL-12 inhibitory activity, and their use in treatment of pain. Applicants therefore respectfully request withdrawal of this rejection.

Enclosed is a check for the Petition for Extension of Time fee to extend the time period for response up to and including November 3, 2003 (as November 1, 2003 is a Saturday). Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 13321-007001.

Respectfully submitted,

Date: November 3, 2003

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